

### In the Specification

Please amend the specification as follows:

Please add the following paragraph at page 7, line 26 as follows:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Please add amend the paragraph beginning at line 27 of page 7 as follows:

**Fig. 1A-1B.** Immunoblot analysis of MRP2 and OATP8 in transfected MDCK cells. Crude membrane fractions from MDCK cells permanently transfected with control vector (MDCK-Co), with human *MRP2* (MDCK-MRP2), with human *OATP8* (MDCK-OATP8), or with both *MRP2* and *OATP8* cDNA (MDCK-MRP2/OAT8) were separated by SDS-PAGE. A, Human MRP2 was detected by the polyclonal antibody EAG5 (Keppler and Kartenbeck 1996; Schaub *et al.*, 1999). B, Human OATP8 was detected by the polyclonal antibody SKT (König *et al.* 2000b). In case of OATP8, only the fully glycosylated form is indicated by an arrowhead, whereas the band is about 90 kDa represents under-glycosylated form of the protein (König *et al.* 2000b).

Please add amend the paragraph beginning at line 4 of page 8 as follows:

**Fig. 2A-2F.** Immunolocalization of recombinant MRP2 and OATP8 in MDCK cells. MDCK cells expressing OATP8 alone (A, D) or both MRP2 and OATP8 (B, C, E, and F) were grown on Transwell membrane inserts and examined by confocal laser scanning microscopy. OATP8 (green fluorescence) and MRP2 (red fluorescence) were stained using the polyclonal antibody SKT (König *et al.* 2000b) and the monoclonal antibody M<sub>2</sub>III6 (Evers *et al.* 1998), respectively. A and B are en face

images focused at the middle of the cell monolayer, C is an en face image focused at the top of the cell monolayer. D, E, and F are vertical sections at the positions indicated by the white lines in A, B, and C. Besides the lateral localization of OATP8, some intracellular staining of this protein can be seen in the vertical sections. Only MRP2 is localized to the apical membrane (E, F). Bar, 10 $\mu$ m.

Please add amend the paragraph beginning at line 31 of page 8 as follows:

**Fig. 4A-4B.** Transcellular transport of [ $^3$ H]BSP. MDCK-Co ( $\Delta$   $\hat{e}$ ), MDCK-MRP2 ( $\blacktriangle$  s), MDCK-OATP8 ( $\square$  e), and MDCK-MRP2/OATP8 ( $\blacksquare$  g) cells were grown on Transwell membrane inserts. [ $^3$ H]BSP (1  $\mu$ M) was given to the basolateral compartments. At the time points indicated, radioactivity in the apical compartments (*Transcellular [ $^3$ H]BSP transport*) and inside the cells (*Transcellular [ $^3$ H]BSP accumulation*) was determined. Total uptake of [ $^3$ H]BSP was calculated as the sum of intracellular and apical radioactivity. Data represent means  $\pm$  SD (n = 4). For most measurements the standard deviation was within the size of the symbols.

Please add amend the paragraph beginning at line 7 of page 9 as follows:

**Fig. 5A-5B.** Vectorial transport and efflux of [ $^3$ H]BSP. MDCK-OATP8 and MDCK-MRP2/OATP8 cells were grown on Transwell membrane inserts. A, Vectorial transport of [ $^3$ H]BSP. [ $^3$ H]BSP (1  $\mu$ M) was given either to the basolateral compartments (B  $\rightarrow$   $\oplus$  A) or to the apical compartments (A  $\rightarrow$   $\oplus$  B). After 15 min at 37°C, radioactivity in the opposite compartments was measured. B, Efflux of [ $^3$ H]BSP. MDCK-OATP8 and MDCK-MRP2/OATP8 cells were incubated with [ $^3$ H]BSP (1  $\mu$ M) in the basolateral compartments at 37°C for 30 min. The cells were then washed with cold buffer and incubated with buffer without [ $^3$ H]BSP at 37°C for 30 min. The radioactivity subsequently released into the basolateral and

the apical compartment and inside the cells was measured. Data represent means  $\pm$  SD (n = 4).

Please add amend the paragraph beginning at line 24 of page 9 as follows:

**Fig. 6A-6C.** HPLC analyses of [ $^3$ H]BSP. MDCK-MRP2/OATP8 cells grown on Transwell membrane inserts were incubated with 1  $\mu$ M [ $^3$ H]BSP in the basolateral compartment at 37°C for 30 min. The medium in the apical compartment and the cell lysate were analyzed by radio-HPLC as described in "Materials and Methods". A, Authentic [ $^3$ H]BSP (Cui *et al.* 2001); B, radioactivity collected in the apical compartment; C, radioactivity accumulated in the cells. [ $^3$ H]BSP (arrow head) and the glutathione S-conjugate of [ $^3$ H]BSP ([ $^3$ H]BSP-SG, arrow) are indicated. Acivicin, an inhibitor of the degradation of the glutathione moiety of [ $^3$ H]BPS-SG, was added to the incubation at a concentration of 5 mM.

Please add amend the paragraph beginning at line 1 of page 10 as follows:

**Fig. 7A-7C.** ATP-dependent transport of [ $^3$ H]BSP by human MRP2. A, Inside-out membrane vesicles from HEK293 cells transfected with human *MRP2* (HEK-MRP2) were incubated with 1  $\mu$ M [ $^3$ H]BSP in the presence of ATP ( $\blacksquare$  g) or 5'-AMP ( $\square$  e). B, Net ATP-dependent transport of [ $^3$ H]BSP into the vesicles from HEK-MRP2 cells ( $\blacksquare$  g) or HEK-Co cells ( $\square$  e) was calculated by subtracting the values determined in the presence of 5'-AMP from those in the presence of ATP. C, The  $K_m$  value of human MRP2 for BSP was determined at BSP concentrations between 1 and 10  $\mu$ M. Data represent means  $\pm$  SD (n = 4).

Please add amend the paragraph beginning at line 14 of page 10 as follows:

**Fig. 8A-8F.** Transcellular transport of organic anions. MDCK-Co, MDCK-OATP8, and MDCK-MRP2/OATP8 cells grown on Transwell membrane inserts were incubated with [ $^3$ H]BSP (1  $\mu$ M), [ $^3$ H]LTC<sub>4</sub> (0.5  $\mu$ M), [ $^3$ H]E<sub>2</sub>17bG (5

$\mu\text{M}$ ), [ $^3\text{H}$ ]DHEAS (5  $\mu\text{M}$ ), Fluo-3 (2  $\mu\text{M}$ ) or [ $^3\text{H}$ ]cholyl taurine (5  $\mu\text{M}$ ) in the basolateral compartments at 37°C. The radioactivity (labeled substrates) or fluorescence (Fluo-3) in the apical compartments was then measured after 30 min. Data represent means  $\pm$  SD (n = 4).

Please add amend the paragraph beginning at line 25 of page 10 as follows:

**Fig. 9A-9H.** Inhibition of the transcellular transport of [ $^3\text{H}$ ]BSP. MDCK-OATP8 (A, C, E, G), and MDCK-MRP2/OATP8 (B, D, F, H) cells grown on Transwell membrane inserts were incubated with [ $^3\text{H}$ ]BSP (1  $\mu\text{M}$ ) in the basolateral compartments in the presence of different concentrations of human serum albumin (HSA, C, D), rifampicin (E, F), or rifamycin SV (G, H). For 2,4-chloro-dinitrobenzene (CDNB) (A, B), cells were pre-incubated with CDNB at room temperature for 20 min, transport of [ $^3\text{H}$ ]BSP was started by replacing the buffer in the basolateral compartments by fresh buffer containing [ $^3\text{H}$ ]BSP and CDNB. After incubation for 30 min at 37°C, the radioactivity in the apical compartments and inside the cells was measured. Data represent means  $\pm$  SD (n = 4).

Please add amend the paragraph beginning at line 14 of page 11 as follows:

**Fig. 11A-11D:** Immunolocalisation of recombinant transport proteins in double-transfected cell lines. MDCKII cells transfected with OAT1 and MRP2 (A, C) or with OATP2 and MRP2 (B, D) were grown on Transwell membrane inserts. Recombinant MRP2 was stained with the antiserum EAG5 (green in A, C) or with the commercial antibody M<sub>2</sub>III6 (red in B, D). Recombinant OAT1 was stained with a commercial monoclonal antibody against an epitope at the carboxyl terminus of OAT1 (red in A, C). Recombinant OATP2 was stained with the polyclonal antiserum ESL (green in B, D). In both double-transfected cell lines, MRP2 was localized to the apical membrane of polarized MDCKII cells. OAT1 and OATP2

were detected only in the basolateral membrane of the respective cell lines.

Please add amend the paragraph beginning at line 17 of page 30 as follows:

~~All publications, patents, and patent documents, cited in this application, are incorporated by reference herein, as though individually incorporated by reference. In the case of any inconsistencies, the present disclosure, including any definitions therein will prevail. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.~~